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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,028	06/22/2006	Nobuyuki Takakura	1254-0318PUS1	4443

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EXAMINER	
KIM, TAEYOON	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
06/30/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/584,028	TAKAKURA ET AL.	
	Examiner	Art Unit	
	Taeyoon Kim	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-26* is/are pending in the application.

4a) Of the above claim(s) *20-22 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-19,23,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 March 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/13/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response filed on 3/13/2009 has been received and entered into the case.

Claim 20-22 have been withdrawn from consideration as being drawn to non-elected subject matter, claims 1-11 are canceled, and claims 23-26 are newly added. Since applicant elected EGF family for species of cytokines, claim 24 is also withdrawn from consideration as being drawn to non-elected subject matter.

Claims 12-19, 23, 25 and 26 have been considered on the merits. All arguments have been fully considered.

Response to Amendment

Specification

The amendment to the specification filed on 3/13/2009 is acknowledged and accepted.

Drawings

The drawings submitted on 3/13/2009 are accepted.

Claim Objections

The claim objection to claim 18 has been withdrawn due to the amendment.

Claim Rejections - 35 USC § 112

The claim rejection under 35 U.S.C.§112, 2nd par., to claim 15 has been withdrawn due to the amendment.

Claim Rejections - 35 USC § 103

Applicant's arguments filed 3/13/2009 have been fully considered but found not persuasive.

In the response, applicant argued that the current invention does not require addition of 5-azacytidine, which is taught by Umezawa et al. Applicant further alleged that the addition of 5-azacytidine is considered to be within the scope of "genetic engineering" since it inhibits DNA methylation, and inhibition of DNA methylation is a treatment for genetic material and alteration in DNA methylation necessarily changes gene expressions in cells.

If the term "genetic engineering" is interpreted broadly to encompass any effect or modulation at the DNA level causing different gene expression, the claimed method of culturing bone marrow cells or cord blood-derived cells with fat tissues or a culture supernatant thereof in the presence of cytokines (e.g. EGF) resulting in differentiation of the cells (thus, changed in gene expression), or mere treatment of cells in culture with various cytokines, growth factors, or other factors which activate signaling pathways and in turn to activate or deactivate gene expression is also considered as genetic engineering, which is contradicting to the claimed invention.

The term "genetic engineering" is interpreted as to any manipulation directly to DNA or genes by introducing, eliminating or changing genes or DNA as supported by the definition given by National Institute of General Medical Science (http://publications.nigms.nih.gov/chemhealth/glossary.html) (p.2 in a box). As Egger et al. particularly define the treatment with 5- azacytidine as "epigenetic" therapy or

treatment, which is not directly introducing, eliminating or changing DNA or genes, rather inhibits DNA methylation and changes the methylation patterns on DNA, it is not considered as "genetic engineering".

Applicant also alleged that Umezawa and Rangappa do not teach or suggest the possibility that fat tissue-derived cells or a culture supernatant thereof may be used to induce differentiation of undifferentiated cells into a myocardial lineage. Applicant further asserted that a person of ordinary skill in the art would not expect the combination of these methods would arrive at the presently claimed invention because there is no predictability or expectation of success from combining these methods.

The argument has been fully considered by found not persuasive.

It is reminded that the rationale to combine two references is not the same of applicant's rationale. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings."); *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972)

(discussed below); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), *cert. denied*, 500 U.S. 904 (1991) (discussed below).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., fat tissue-derived cells or a culture supernatant thereof may be used to induce differentiation of undifferentiated cells into a myocardial lineage) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore, since the effect of fat-derived cells or a culture condition thereof may induce differentiation of bone marrow or cord blood derived cells as argued by applicant is an intrinsic property of the fat-derived cells or a culture condition thereof, the fat-derived mesenchymal stem cells of the method of Umezawa et al. in view of Rangappa et al. would have the same effect.

The discovery of a new use for an old structure based on unknown properties of the structure *might* be patentable to the discoverer as a process of using. *In re Hack*, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957). However, when the claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. *In re May*, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978) and *In re Tomlinson*, 363 F.2d 928, 150 USPQ 623 (CCPA 1966). See M.P.E.P. § 2112.02.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-19, 23, 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The current claims are drawn to the method of differentiating bone marrow cells or cord blood-derived cells into myocardial precursor cells or myocardial cells by culturing the cells with cells isolated from fat tissues.

It is vague what subject matter the phrase of "under conditions wherein said bone marrow ... myocardial cells" intends to point out.

It is not clear whether the claims require an additional "condition" which also induces differentiation of bone marrow cells or cord blood-derived cells into myocardial precursor cells or myocardial in addition to the claimed method step of co-culturing bone marrow or cord blood-derived cells with fat tissue-derived cells, or the condition refers to the step of co-culturing the bone marrow cells or cord blood-derived cells with fat-tissue derived cells per se. Clarification is required.

For search purpose, the co-culturing step per se is considered as the condition.

The limitation in claim 18 drawn to a ratio of 1:1 to 10 is not clear whether it is meant be 1:1 to 1:10 or 1:1 to 10:1. Clarification is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all

obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-19, 23, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Umezawa et al. (US 2002/0142457; IDS ref.) in view of Rangappa et al. (2003, Ann. Thorac. Surg.) in further view of Egger et al. (2004, Nature), Bonnet (2003, Clin. Exp. Med), Gilmore et al. (2000, Exp. Hematol.) and Lee et al. (2004, Blood).

Umezawa et al. teach a method of differentiating multipotential stem cells from bone marrow or umbilical cord blood derived cells into cardiomyocyte in vitro (par. 11, 12, 17-19).

Umezawa et al. teach that the cells having the potential to differentiate into cardiomyocytes are cultured for 24 hours in the presence of 5-azacytidine, and then further cultured for 2-3 weeks to obtain cardiomyocytes (par. 134), satisfying the

limitation of claim 13.

Umezawa et al. teach the expression of a-skeletal actin and a-cardiac actin (sarcomeric actin) in the cardiomyocytes differentiated from bone marrow (par. 330), and thus meet the limitation of claim19.

Umezawa et al. do not teach co-culture of fat tissue derived cells or a culture supernatant of the fat tissue-derived cells with bone marrow cells or cord blood derived cells, respectively.

Rangappa et al. teach a method of differentiating fat-derived mesenchymal stem cells (MSCs) into cardiomyocytes (Abstract).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to combine bone marrow or cord blood derived multipotential stem cells of Umezawa et al. with adipose-derived stroma stem cells of Rangappa et al. in the method of myocardial differentiation of the MSCs. This is because the method of differentiating bone-marrow or cord-blood derived mesenchymal stem cells into cardiomyocytes of Umezawa et al. is identical to the method of differentiating adipose-derived stromal MSCs of Rangappa et al. such that both methods utilize 5-azacytidine to induce the mesenchymal stem cells into cardiomyocytes (par. 12 and 43 of Umezawa et al., and p.776, right col. of Rangappa et al.). Since both bone marrow or cord blood derived multipotential stem cells and fat-tissue derived MSCs can be differentiated into cardiomyocytes upon the treatment with 5-azacytidine (a cardiomyogenic differentiating factor), the combined stem cell populations would be also differentiated into cardiomyocytes under the same method

steps.

It is well established that duplicating components with similar functions within a composition is obvious; see *In re Harza*, 274 F.2d 669, 124 USPQ 378 (CCPA 1960) and M.P.E.P. § 2144.04. The multipotential stem cells of bone marrow or cord blood, and MSCs of fat tissue are considered to have similar functions to differentiate into cardiomyocytes, it would have been obvious to combine two cell populations in the method of differentiating into cardiomyocytes.

Since the method of Umezawa et al. in view of Rangappa et al. utilize 5-azacytidine, this is considered to satisfy the new limitation of a condition which induces bone marrow cells or cord blood-derived cells to myocardial cells.

With regard to the limitation of "without genetic engineering", the treatment with 5-azacytidine to the mesenchymal stem cells is not considered as a genetic engineering. Rather it is considered as epigenetic modification since 5-azacytidine is a DNA methylation inhibitor according to Egger et al. (Abstract and Table 2).

With regard to the limitation of using a culture supernatant of fat tissue-derived cells in the method of differentiating bone marrow cells or cord blood-derived cells, Umezawa et al. teach that the differentiation of cells having a potential to differentiate into cardiomyocytes can be induced by a culture supernatant of such cells (par. 105, 106, 132). Since the fat tissue-derived MSCs of Rangappa et al. is considered as a cells having a potential to differentiate into cardiomyocytes, it would have been obvious to a person of ordinary skill in the art to use a cell culture supernatant of MSCs derived from fat tissues of Rangappa et al. in the method of Umezawa et al. utilizing a culture

supernatant in induction of differentiation of bone marrow cells or cord blood-derived cells into cardiomyocytes.

With regard to the limitation of using cytokines in the method of claims 14, 15 and 23, Umezawa et al. teach the use of growth factors or cytokines such as PDGF, FGF-8 (EGF family member), ET-1 or BMP-4 for differentiation of the mesenchymal stem cells into cardiomyocytes (par. 46-48).

With regard to the limitation to the bone marrow cells being MSCs or HSCs in claim 16, it is well known in the art that bone marrow cells comprise both HSCs and MSCs according to Bonnet (entire document), and thus the multipotential stem cells of bone marrow of Umezawa et al. inherently comprise HSCs as well as MSCs.

With regard to the limitation of ratio between bone marrow cells and fat tissue derived cells being 1:1 to 1:10 in claim 18 or 1:4 as in claim 26, it would have been obvious to a person of ordinary skill in the art to optimize the ratio between bone marrow cells and fat tissue derived cells for the method of Umezawa et al. in view of Rangappa et al. This is because a person of ordinary skill in the art would recognize that the mixing ratio between two groups of cell population in co-culture system would be considered as a result effective variable for the method. The variables would be routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by those references. Generally, differences in concentration, and thus the ratio of the contents, will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover

the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); ** In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made especially in the absence of evidence to the contrary.

With regard to the limitation to the cord blood-derived cells being mononuclear cells in claim 17, Umezawa et al. is silent which cells the multipotential stem cells (mesenchymal stem cells) of umbilical cord blood is derived from. However, it is well known in the art that multipotential stem cells, including HSCs and MSCs according to Bonnet, can be derived from umbilical cord blood-derived mononuclear cells according to Gilmore et al. (p.1298, Materials and Method) and Lee et al. (see p.1670, MSC isolation and culture). Thus, the multipotential stem cells of Umezawa et al. would be inherently derived from mononuclear cells of umbilical cord blood.

With regard to the limitation drawn to the bone marrow cells or cord blood-derived cells being derived from the same species as the fat tissues, it is submitted that

since it is extremely well known in the art that the cells derived from the method of Umezawa et al. in view of Rangappa et al. can be used for transplantation for repairing or reconstructing myocardium (par. 3 of Umezawa et al.; p.775, left col. of Rangappa et al.), it would have been obvious to a person of ordinary skill in the art to combine the cells from the same species (allogeneic) or even autologous sources for the use of the cells in myocardial repair.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taeyoon Kim whose telephone number is (571)272-9041. The examiner can normally be reached on 8:00 am - 4:00 pm ET (Mon-Thu).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Taeyoon Kim/
Primary Examiner, Art Unit 1651